Original paper

The impact of a vaginal brachytherapy boost to pelvic radiation in stage III endometrial cancer

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Abstract

Purpose: We investigate the use and impact of a vaginal brachytherapy boost (VBB) after pelvic radiotherapy for stage III endometrial adenocarcinoma on vaginal and pelvic control.

Material and methods: One hundred patients treated from 1998-2011 with surgery and adjuvant therapy with or without a VBB were included. Variables examined were grade, stage, lymphovascular space invasion (LVSI), vaginal involvement (VI), cervical stromal involvement (CSI), myometrial invasion (MI), and a VBB. Failure was scored as vaginal, or pelvic. Fisher's exact test assessed association between variables with vaginal and pelvic control.

Results: With a median follow up of 43 months, 31% were stage IIIA, 6% stage IIIB, and 63% stage IIIC. Thirty-eight (38%) received pelvic radiotherapy alone, and 62% received adjuvant chemotherapy. Of the 100 patients, 82 were treated with a VBB, 10 were not treated with a VBB, and 8 were not treated with RT. Of the 82 patients who received a VBB, 5 failed in the vagina with vaginal and pelvic control rates of 94% and 92%. The impact of VB reached borderline significance with its impact on pelvic control, 92% vs. 70% ($p = 0.056$), and did not affect vaginal control, 94% and 90% ($p = 0.50$). Neither tumor grade, LVSI, CSI, stage, nor LVSI ($p > 0.05$) statistically significantly impacted vaginal control.

Conclusions: There are no clinical guidelines for the use of a VBB in stage III endometrial cancer. The majority of our patients were treated with a VBB and experienced excellent pelvic and vaginal control. The presence of traditional adverse features did not negatively impact control in our patient cohort. However, the role of a VBB needs further investigation to understand the incremental benefit beyond pelvic RT.

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Key words: endometrial cancer, pelvic radiation therapy, vaginal brachytherapy.

Purpose

Endometrial cancer is the most common female malignancy of gynecologic origin with an estimated incidence of 47,130 new cases and 8,010 deaths in 2012 [1]. Unfortunately, there has been little change in 5-year overall survival rates since the mid 1970's. The management of endometrial cancer therefore continues to evolve with refinement of both surgical approaches and adjuvant therapy. Surgery remains the indisputable standard of care for initial management of uterine disease. Various approaches continue to be utilized for management of locally advanced endometrial cancer, especially for women with regional lymph node involvement. It has been well established that women with FIGO stage III endometrial cancer benefit from adjuvant therapy in the form of chemotherapy and radiotherapy to improve local control, disease free survival and overall survival outcomes [2-6]. Often a matter of institutional preference, these modalities are used independently or in some sequential combination, as both have shown benefit albeit with continual debate surrounding ideal order and timing of these therapies [6].

An unanswered question is whether women with stage III disease who receive whole pelvis radiation therapy (WPRT) as part of their adjuvant therapy derive meaningful benefit from the addition of a vaginal brachytherapy boost (VBB). Currently, there is limited data addressing the need for vaginal brachytherapy as a compliment to pelvic radiotherapy or systemic chemotherapy in stage III endometrial cancer patients. This investigation examines the impact of a VBB on disease control, using patients treated with adjuvant WPRT with or without vaginal brachytherapy following optimal surgery for International Federation of Obstetrics and Gynecology (FIGO) stage III endometrial cancer. Currently, there are no guidelines for clinicians on when to consider a VBB. Our primary study endpoints include the impact

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of a VBB on pelvic and vaginal control. We also explore the risk factors associated with the selection of a VBB.

Material and methods

The institutional tumor registry and departmental databases were queried to identify patients who were consecutively and definitively treated for FIGO stage III endometrial adenocarcinoma, clear cell or serous cancer between 1998 and 2012. The Institutional Review Board granted permission for this study. Patient characteristics considered included age, race, Karnofsky performance status, ethnicity, and medical comorbidities including the presence of diabetes and hypertension. The pathological tumor characteristics included FIGO stage, degree of myometrial invasion, cervical stromal involvement, lymphovascular space invasion, grade, adnexal and vaginal involvement, and status of pelvic and paraaortic lymph nodes. Treatment characteristics included type and number of chemotherapy cycles given, external beam dose, treatment modality, and vaginal brachytherapy dose. Outcome measures were local control, vaginal, and pelvic control.

A total of 100 consecutive patients were treated from 1998 to 2012 were included in the analysis. All patients underwent a total abdominal, laproscopic, or robotic assisted hysterectomy, and bilateral salpingo-oophorectomy with either lymphadenectomy or lymph node sampling, peritoneal washings and omental biopsy. Patients had their pathology reviewed by a specialist in the field of gynecological cancer. One patient was treated preoperatively and was subsequently lost to follow-up. Descriptive analyses were performed to characterize the clinical, demographic, and pathological features of the patient population. Assessed variables include performance status, tumor grade, pathologic T stage, N stage, lymphovascular space invasion (LVSI), vaginal involvement (VI), lower uterine segment invasion (LUS), cervical stromal involvement (CSI), myometrial invasion (MI), and use of a VBB. Failure was scored as vaginal, pelvic, abdominal or distant. Fisher's exact tests were used to assess the association between these variables on vaginal and pelvic control.

Results

Patient characteristics

As shown in Table 1, of the 100 patients, 13% were Latino, 43% white, and 8% black. Also 69% had a Karnofsky performance status of 90 or 100. In terms of medical comorbidity, 48% has diabetes and 52% had hypertension. Table 2 presents the tumor characteristics of the patients. The stages of the patients were 31 stage IIIA, 6 stage IIIB, 39 stage IIIC1, and 24 stage IIIC2. In addition, 77% of the population was adenocarcinoma and 57% had LVSI, 30% had adenexal involvement, 43% had LUS involvement, 31% CSI, and 8% had VI as shown in Table 2.

Treatment

Of the 100 patients, 82 were treated with WPRT and a VBB, 10 were treated with WPRT alone (no VBB), and 8 were not treated with RT. In the analysis, 92 patients were treated with whole pelvic radiation for a total dose of 45-50.4 Gy in 1.8-2 Gy per fraction. A single patient was treated with whole abdominal radiotherapy to a dose of 30 Gy followed by a boost of 19.8 Gy to the pelvis alone. The average elapsed time for the external beam was 39 days. Three dimensional conformal radiation therapy was the primary method of external beam radiotherapy with the use of intensity modulated radiation therapy increasing over the course of the study period. Sixty-two percent of patients were also treated with systemic chemotherapy, the majority with carboplatin and paclitaxel for an average of 5 cycles, while cisplatin as a single agent was used in 3 patients.

Among all patients, 82 patients were treated with a VBB using a high dose rate Ir-192 afterloader. Brachytherapy was delivered to the upper one-third to one-half of the vagina and was prescribed to either the surface

Table 1. Patient characteristics

Patients (*n*)	100
Ethnicity	
Hispanic or Latino	13
Not Hispanic or Latino	70
Unknown/Not reported	17
Race	
American Indian/Alaska Native	0
Asian	6
Native Hawaiian or other Pacific Islander	3
Black or African American	8
White	43
More than one race	0
Unknown/Not reported	40
Performance Status	
50	1
60	3
70	10
80	14
90	52
100	17
Diabetes	
Yes	48
No	52
Hypertension	
Yes	52
No	48

Table 2. Tumor characteristics

Tumor characteristics	Patient number
Patient pathologic stage (FIGO)	
IIIA	31
IIIB	6
IIIC1	39
IIIC2	24
Patient pathologic T stage (AJCC)	
T1a	16
T1b	27
T2	9
T3a	35
T3b	13
Patient pathologic N stage	
N0	38
N1	37
N2	25
Patient pathologic M stage	
0	99
1	1
Tumor histology	
Adenocarcinoma	77
Carcinosarcoma	8
Clear cell carcinoma	4
Papillary serous carcinoma	11
Lymphovascular space invasion	
Yes	57
No	41
Location of positive nodes	
Pelvic	40
Paraaortic	20
Adnexal involvement	
Yes	30
No	69
Parametria involvement	
Yes	15
No	85
Vaginal involvement	
Yes	8
No	92
Positive pelvic wash	
Yes	12
No	87
Tumor grade	
1	28
2	26
3	0
Lower uterine involvement	
Yes	43
No	57
Cervical stroma involvement	
Yes	31
No	69
Cervical gland involvement	
Yes	35
No	64
Patient's margin status	
Negative	92
Close (< 5 mm)	2
Positive	5

or to 0.5 cm. Starting in 2009, all patients treated with brachytherapy had image simulation. This verification was a quality control measure to account for accuracy of the measured distended vaginal length and proper applicator placement within the pelvis as shown in Figure 1. Most patients received 12-15 Gy in 3 fractions over the course of 7-14 days.

Outcomes

The median follow up time was 43 months. Among the 100 patients available for disease related outcome analysis, 94 patients experienced vaginal control. There was no statistically significant association between vaginal control and a brachytherapy boost ($p = 0.51$). Of those treated with a brachytherapy boost, 82 patients (94%) experienced vaginal control. Of those who failed in the vagina, 5 of 6 were treated with a VBB. There were no statistically significant differences in vaginal control when examining pathologic variables such as grade, LVSI, CSI, MI, or LUS involvement in the population as shown in Table 3. In 8 patients who had VI, one experienced vaginal failure. There was no statistical difference in rates of vaginal control based on vaginal involvement ($p = 0.40$).

Ten percent of patients failed in the pelvis as defined by failure in the pelvis and/or vagina, 7 of which were treated with a vaginal brachytherapy boost. For patients who experienced pelvic control, 93% were treated with a VBB. There was a trend for increasing pelvic control with the use of a boost, $p = 0.056$. There was no statistically significant increase in pelvic failure based on LVSI, lymph node status, CSI, VI, or LUS involvement as shown in Table 3. During the follow up period, 11% recurred with distant metastatic disease, 15% in the para-aortic or pelvic lymph nodes, 13% failed in the abdomen.

Discussion

Adjuvant therapy for locally advanced endometrial cancer continues to evolve. Our study seeks to understand the utility of a VBB, review the existing literature on stage 3 endometrial cancer outcomes, and explore the potential benefit of a VBB on vaginal and pelvic control. There is paucity in the literature regarding the addition of a VBB to whole pelvic radiation in this group of patients, and who may benefit from this additional therapy to whole pelvic radiation.

For patients with stage III endometrial cancer, the attention to pelvic control is relevant. With the publication of GOG 122 in 1995, adjuvant systemic chemotherapy was, in many regards, considered the new standard of care after demonstrating an overall survival benefit of systemic therapy over whole abdominal radiation at 5 years [7]. However, in the systemic therapy group, the risk of relapse in the pelvis neared 20% [7]. Furthermore, several single institution studies have shown increased rates of pelvic relapse much higher than was demonstrated in GOG 122 [7-10]. In fact, Mundt *et al*. showed a pelvic recurrence rate of 47% in high risk pathologic endometrial adenocarcinoma treated with adjuvant chemotherapy and no radiation therapy. In addition, Klopp *et al*. published their single institutional data confirming a high rate of pelvic failure in those receiving chemotherapy alone [8]. In this series, five-year pelvic-relapse-free survival (98% vs. 61%, $p = 0.001$), DSS (78% vs. 39%, $p = 0.01$), and overall survival (73% vs. 40%, $p = 0.03$) were significantly better for the regional RT group than the systemic therapy group [8]. Another study by Secord *et al*. reviewed 256 patients with stage IIIC endometrial cancer [6]. The three-year RFS was 56% for chemotherapy alone, compared to 73% for radiation alone, and 73% for combination therapy ($p = 0.12$). Those receiving chemotherapy alone had the worst 3-year OS (78%) compared to either radiotherapy alone (95%), or combination therapy (90%) ($p = 0.005$) [6]. They conclude that radiation alone or chemotherapy and radiation was associated with improved outcomes for patients with optimally resected stage IIIC adenocarcinoma compared to those treated with chemotherapy only [6]. Therefore, the risk of vaginal and pelvic control remains an issue in patients treated with chemotherapy alone, arguing for a role of consolidative radiation therapy.

Our study is one of the largest in the literature to review stage III endometrial cancer related outcomes, and the only institutional data specifically investigating the role of a brachytherapy boost in this population. The role of a VBB remains controversial with wide differences in practice pattern variation. In a recent SEER analysis of stage IIIC endometrial adenocarcinoma, 51% were treated with adjuvant pelvic radiation and 21% were given a brachytherapy boost [11]. Even in the ongoing cooperative group trials, such as the current GOG 258, which randomizes stage III patients to chemotherapy alone versus chemoradiation followed by systemic therapy, the addition of vaginal brachytherapy is at the discretion of the treating physician. Depending on the instution of treatment, patients are often offered a vaginal brachytherapy boost in the setting of LVSI, high grade disease, VI, or CSI. There also remains debate on the amount of vagina to include in the brachytherapy boost field. The majority of our patients were treated to the upper half of the vagina, based on a vaginal measurement that was performed in the clinic prior to brachytherapy.

One of the major factors in the decision to give a VBB is the potential risk of additional complications. As re-

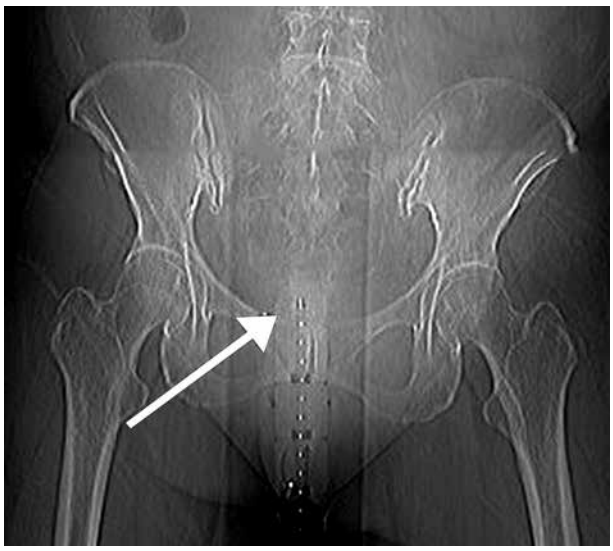

Fig. 1. Image verification of a vaginal brachytherapy implantation

Table 3. Pathological characteristic variables on pelvic and vaginal control using the Fisher's exact test for significance

Pathologic characteristic	Pelvic control *p*-value	Vaginal control *p*-value
VBB	0.056	0.508
LVSI	0.462	1
Cervical Involvement	0.495	0.370
Grade	0.691	0.759
Lymph node status	0.915	0.764
Vaginal involvement	0.583	0.401
Lower uterine segment	0.741	0.397

VBB – vaginal brachytherapy boost, LVSI – lymphovascular space invasion

ported in the literature, there is an acceptable rate of reported toxicity with the addition of a VBB. Klopp *et al*. described the major complications in stage 3 endometrial cancer after pelvic radiation with 86% of patients receiving a VBB [8]. There was one grade 4 small bowel obstruction in a patient treated with external beam RT, for an overall radiation-related major complication rate of 2% [8]. Rates of minor complications were not recorded [8]. In the RTOG trial 97-08, 22% of endometrial cancer patients had stage IIIC [12]. The treatment for the 46 patients on trial was surgery followed by adjuvant concurrent chemoradiotherapy. Patients received whole pelvis RT to 45 Gy followed by a VBB, with cisplatin (50 mg/m^2) administered on days 1 and 28, followed by four courses of cisplatin (50 mg/m^2) and paclitaxel (175 mg/m^2) [12]. At 4 years, the reported late toxicity for this regimen was grade 1 in 16%, grade 2 in 41%, grade 3 in 16%, and grade 4 in 5% [12].

In our study, there was a trend for increased pelvic control in those who had VI and were boosted with brachytherapy. Eighty-two of the one hundred patients in the study were treated with a VBB to achieve a vaginal control rate of 94% and pelvic control rate of 90%. This control rate is impressive given that 57% had LVSI, 30% had adenexal involvement, 43% had LUS involvement, 31% CSI, and 8% had VI. In addition, the vast majority of our patients had lymph node involvement. In the SEER analysis, the addition of a radiation therapy improved survival in those with stage IIIC endometrial cancer with direct tumor extenstion with a 5 year overall survival rate of 34%, 47%, and 63% in those receiving adjuvant chemotherapy alone, external beam radiation, and a vaginal brachytherapy boost [11]. Furthermore, when direct extension of the primary tumor was present, the addition of brachytherapy conferred a greater survival advantage [11]. In our population, there was a trend for improved vaginal control in those who had vaginal involvement, but there was no effect of the VBB in respect to margin status. Furthermore, our study population experienced a high vaginal control rate, 94%, and pelvic control, 90% with the majority of patients treated with trimodality therapy: chemotherapy, consolidative pelvic radiation, and a VBB.

The ongoing question in the field is the questionable incremental benefit of additional radiation to the vaginal apex. Is the addition of vaginal brachytherapy clinically significant for reducing apex recurrences? Should it be given to all patients with stage III endometrial adenocarcinoma? Unfortunately, our data is not able to definitively answer this question. A limitation of our study is that a high number of patients were treated with a brachytherapy boost, reflecting the decision of the physician to deliver a boost in the majority of cases. Therefore, our paper is intended to be thought provoking on the selection and role of a vaginal brachytherapy boost in this defined patient population. Our study reports a low percentage of locoregional failure. Therefore, we are unable to illustrate risk factors that could potentially predict for vaginal failure, and thus warrant the use of a VBB. Perhaps the combination of systemic therapy and radiation therapy are altering the patterns of failure, and the vaginal control would be sufficient without the additional therapy. In terms of patterns of failure, a phase III trial of adjuvant chemotherapy versus pelvic radiotherapy was conducted by Maggi *et al*. After a median follow-up was 95.5 months, it failed to replicate the results of GOG 122 and revealed no statistical difference in overall survival or progression free survival. The chemotherapy arm trended towards delayed metastatic disease and the radiotherapy arm trended towards improved local control, but neither achieved statistical significance. However, this trial did not report use of vaginal brachytherapy. Compared to single institutional data and the results of GOG 122, our patients had improved vaginal and pelvic control consistent with a recently published retrospective review from Brigham and Women's Hospital, which examined the outcomes of patients treated with adjuvant therapy for FIGO IIIC endometrial adenocarcinoma [3,4,6,7,9,10].

Conclusions

There is no consensus on the addition of a VBB in stage 3 endometrial carcinoma. The majority of our patients with stage III endometrial cancer were treated with a VBB, and experienced excellent pelvic and vaginal control. There was no difference between pelvic or vaginal control with the addition of a VBB. However, the presence of high grade, VI, LVSI, CSI did not adversely affect outcomes in our patient cohort, suggesting that the role of a VBB in this population needs further exploration.

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Disclosure

Authors report no conflict of interest.

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